CLAIMS

1. A process for the preparation of a depolymerized-LMW-epiK5-N,O-sulfate containing 40%-60% iduronic units and having a sulfation degree of from 2.3 to 2.9, which comprises

(a) treating a tertiary or quaternary organic base salt of a depolymerized-LMW-epiK5-N-sulfate containing 40%-60% iduronic units with a sulfation agent under O-oversulfation conditions to obtain a depolymerized-LMW-epiK5-amine-O-oversulfate;

(b) submitting the depolymerized-LMW-epiK5-amine-O-oversulfate thus obtained to a selective O-desulfation to obtain a depolymerized-LMW-epiK5-amine-O-sulfate;

(c) treating a tertiary or quaternary organic base salt of the depolymerized-LMW-epiK5-amine-O-sulfate thus obtained with a O-sulfation agent to obtain a depolymerized-LMW-epiK5-amine-O-sulfate containing at least 80% 6-O-sulfate;

(d) submitting the depolymerized-LMW-epiK5-amine-O-sulfate containing at least 80% 6-O-sulfate thus obtained to a N-sulfation reaction and isolating the depolymerized-LMW-epiK5-N,O-sulfate thus obtained.

2. Process according to claim 1, wherein the depolymerized-LMW-epiK5-N,O-sulfate thus obtained is isolated as the sodium salt thereof which is optionally converted into another pharmaceutically acceptable salt thereof.

3. Process according to claim 2, wherein said other salt is that with another alkaline metal, an alkaline-earth metal, aluminum or zinc.

4. Process according to anyone of claims 1 to 3, wherein the starting depolymerized-LMW-epiK5-N-sulfate is obtained by submitting a K5-N-sulfate, in any order,

(i) to C5-epimerization with a D-glucuronyl C5-epimerase isolated, purified and either in solution or immobilized on a solid support, at a pH of approximately 7, at a temperature of approximately 30°C and for a time period of 12-24 hours in the presence of at least one bivalent ion selected among calcium, magnesium, barium and manganese; and

(ii) to a nitrous depolymerization followed by reduction, normally with sodium borohydride.

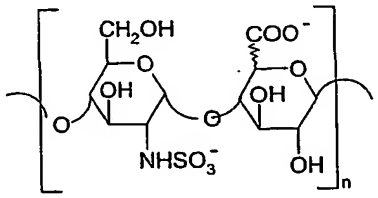
5. Process according to claim 4, wherein the starting depolymerized-LMW-epiK5-N-sulfate is obtained according to the sequence (i)-(ii) and has a mean molecular weight of from about 1,500 to about 12,000.

6. Process according to claim 5, wherein, said mean molecular weight is from about 1,500 to about 7,500.

7. Process according to claim 4, wherein the starting depolymerized-LMW-epiK5-N-sulfate is obtained according to the sequence (ii)-(i) and has a mean molecular weight of from about 4,000 to about 12,000.

8. Process according to claim 7, wherein said molecular weight is of from about 5,000 to about 7,500.

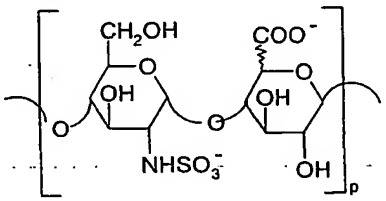
9. Process according to anyone of claims 1 to 8, wherein the starting depolymerized-LMW-epiK5-N-sulfate consists of a mixture of chains in which at least 90% of said chains has the formula I



(I)

in which 40%- 60% of the uronic units are those of iduronic acid, n is a integer from 2 to 20 and the corresponding cation is chemically or pharmaceutically acceptable.

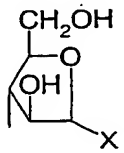
10. Process according to anyone of claims 1 to 9, wherein said starting depolymerized-LMW-epiK5-N-sulfate consists of a mixture of chains in which the preponderant species has the formula I'a



(I'a)

wherein 40% to 60% of the uronic units are those of iduronic acid and p is an integer from 4 to 8.

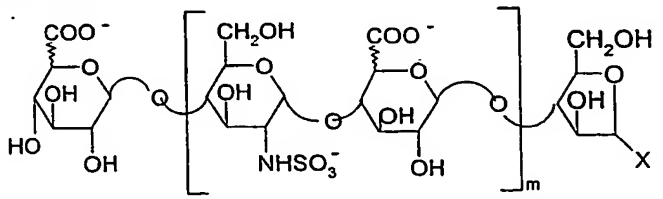
11. Process according to anyone of claims 1 to 10, wherein said starting depolymerized-LMW-epiK5-N-sulfate presents a 2,5-anhydromannitol unit of structure (a)



(a)

in which X represents a hydroxymethyl group, at the reducing end of the majority of the chains in said mixture of chains.

12. Process according to anyone of claims 9 to 11, wherein said starting depolymerized-LMW-epiK5-N-sulfate consists of a mixture of chains in which the preponderant species has the formula I'b



(I'b)

in which X hydroxymethyl, m is 4, 5 or 6, the corresponding cation is a chemically or pharmaceutically acceptable ion and the glucuronic and iduronic units are present alternately, the non reducing extremity being a glucuronic or iduronic unit, with a ratio glucuronic/iduronic from 45/55 to 55/45.

13. A process for the preparation of depolymerized-LMW-K5-N,O-sulfates having a sulfation degree of from 2.3 to 2.9 and of their pharmaceutically acceptable salts, which comprises

(ii) submitting a K5-N-sulfate to a nitrous depolymerization to obtain a depolymerized-LMW-K5-N-sulfate having a mean molecular weight higher than 4,000;

(i) submitting the depolymerized-LMW-K5-N-sulfate thus obtained to a C5-epimerization with D-glucuronyl-C5-epimerase to obtain a depolymerized-epiK5-N-sulfate containing from 40% to 60% iduronic units;

(a) treating a tertiary or quaternary organic base salt of the depolymerized-LMW-epiK5-N-sulfate thus obtained with a sulfation agent under the conditions of O-oversulfation to obtain a depolymerized-LMW-epiK5-amine-O-oversulfate;

(b) submitting the depolymerized-LMW-epiK5-amine-O-oversulfate thus obtained to a selective O-desulfation to obtain a depolymerized-LMW-epiK5-amine-O-sulfate;

(c) treating a tertiary or quaternary organic base salt of the depolymerized-LMW-epiK5-amine-O-sulfate thus obtained with a O-sulfation agent to obtain a depolymerized-LMW-epiK5-amine-O-sulfate containing at least 80% 6-O-sulfate;

(d) submitting the depolymerized-LMW-epiK5-amine-O-sulfate containing at least 80% 6-O-sulfate thus obtained to a N-sulfation reaction and isolating the depolymerized-LMW-epiK5-N,O-sulfate thus obtained as the sodium salt thereof which is optionally converted into another pharmaceutically acceptable salt.

14. Process according to claim 13, wherein at the end of step (ii) a depolymerized-LMW-K5-N- sulfate having a mean molecular weight of from about 5,000 to about 7,500 is obtained.

15. Process according to claim 13, wherein at the end of step (ii) a depolymerized-LMW-K5-N- sulfate having a mean molecular weight of from about 6,000 to about 7,500 is obtained.

16. A process for the preparation of depolymerized-LMW-K5-N,O-sulfates having a sulfation degree of from 2.3 to 2.9 and of their pharmaceutically acceptable salts, which comprises

(i) submitting a K5-N-sulfate to a C5-epimerization with a D-glucuronyl C5-epimerase isolated, purified and in solution or immobilized on a solid support, at a pH of about 7, at a temperature of about 30°C and for a period of time of 12-24 ore in the presence of at least one bivalent ion selected among calcium, magnesium, barium and manganese;

(ii) submitting the epiK5-N-sulfate thus obtained to a nitrous depolymerization followed by a reduction, normally with sodium borohydride, to obtain a depolymerized-LMW-K5-N-sulfate;

(a) treating a tertiary or quaternary organic base salt of the depolymerized-LMW-epiK5-N-sulfate thus obtained with a sulfation agent under O-oversulfation conditions to obtain a depolymerized-LMW-epiK5-amine-O-oversulfate;

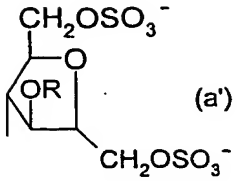
(b) submitting the depolymerized-LMW-epiK5-amine-O-oversulfate thus obtained to a selective O-desulfation to obtain a depolymerized-LMW-epiK5-amine-O-sulfate;

(c) treating a tertiary or quaternary organic base salt of the depolymerized-LMW-epiK5-amine-O-sulfate thus obtained with an O-sulfation agent to obtain a depolymerized-LMW-epiK5-amine-O-sulfate containing at least 80% 6-O-sulfate;

(d) submitting the depolymerized-LMW-epiK5-amine-O-sulfate containing at least 80% 6-O-sulfate thus obtained to a N-sulfation reaction and isolating the depolymerized-LMW-epiK5-N,O-sulfate thus obtained as the sodium salt thereof which is optionally converted into another pharmaceutically acceptable salt.

17. A depolymerized-LMW-epiK5-N,O-sulfate obtainable according to anyone of claims 1 to 16.

18. A depolymerized-LMW-epiK5-N,O-sulfate having a sulfation degree of from 2.3 to 2.9, a mean molecular weight of from about 1,500 to about 12,000 and, at the reducing end of the majority of its chains, the structure (a')



(a')

in which R represents hydrogen or SO_3^-, or a pharmaceutically acceptable salt thereof.

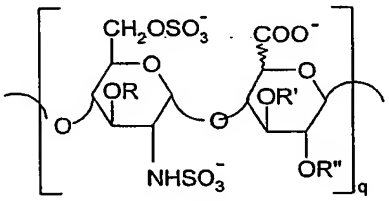
19. A depolymerized-LMW-epiK5-N,O-sulfate according to claim 18, having a mean molecular weight of from about 1,500 to about 8,000 and a sulfation degree from 2.5 to 2.9.

20. A depolymerized-LMW-epiK5-N,O-sulfate according to claim 19, having a sulfation degree of from 2.7 to 2.9.

21. A depolymerized-LMW-epiK5-N,O-sulfate according to claim 20, having a mean molecular weight of about 6,000.

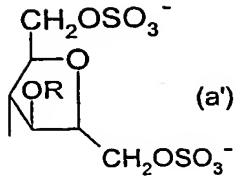
22. A depolymerized-LMW-epiK5-N,O-sulfate according to anyone of claims from 18 to 21, having a mean molecular weight of about 6,000, a sulfation degree of from 2.7 to 2.9, a content of 80%-95% in glucosamine 6-O-sulfate, of 95%-100% in glucosamine N-sulfate, of 45%-55% in glucosamine 3-O-sulfate, of 35%-45% in glucuronic acid 3-O-sulfate, of 15%-25% in iduronic acid 2-O-sulfate and presenting an unity (a') at the reducing end of the majority of its chains, or a pharmaceutically acceptable salt thereof.

23. A depolymerized-LMW-epiK5-N,O-sulfate according to claim 18 consisting of a mixture of chains in which at least 80% of said chains has the formula III



(III)

wherein the 40%-60% of the uronic units are those of iduronic acid, q is an integer from 2 to 17, R, R' and R" are hydrogen or SO_3^- for a sulfation degree of from 2.3 to 2.9, and the reducing end of the majority of the chains in said mixture of chains presents a sulfated 2,5-anidromannitol unit of structure (a')



in which R represents hydrogen or SO_3^- and the corresponding cation is chemically or pharmaceutically acceptable.

24. A depolymerized-LMW-epiK5-N,O-sulfate according to claim 23, consisting of a mixture of chains in which at least 80% of said chains has the formula III wherein q is an integer from 2 to 14.

25. A depolymerized-LMW-epiK5-N,O-sulfate according to claim 23, consisting of a mixture of chains in which at least 80% of said chains has the formula III wherein q is an integer from 2 to 11.

26. A depolymerized-LMW-epiK5-N,O-sulfate according to claim 23, consisting of a mixture of chains in which the preponderant species is a compound of formula III wherein q is 8 or 9, R is 45%-55% SO_3^-, R' is 35%-45% SO_3^- in glucuronic acid, R" is 15%-25% SO_3^- in iduronic acid, for a sulfation degree of from 2.7 to 2.9.

27. Pharmaceutical composition comprising, as an active ingredient, a pharmacologically active amount of a depolymerized-LMW-epiK5-N,O-sulfate according to anyone of claims 17 to 26, or of a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutical carrier.

28. A method for the regulation of the coagulation in a mammal, which comprises administering to said mammal in need of said regulation of the coagulation an effective amount of a depolymerized-LMW-epiK5-N,O-sulfate according to anyone of claims 17 to 26 or of a pharmaceutically acceptable salt thereof.

29. A method for preventing or treating thrombosis in a mammal, which comprises administering to said mammal an effective amount of a depolymerized-LMW-epiK5-N,O-sulfate according to anyone of claims 17 to 26 or of a pharmaceutically acceptable salt thereof.

30. The method of claim 28, wherein said effective amount is administered in a pharmaceutical composition comprising from 5 to 100 mg of said depolymerized-LMW-epiK5-N,O-sulfate or of a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutical carrier.

31. The method of claim 29, wherein said effective amount is administered in a pharmaceutical composition comprising from 5 to 100 mg of said

depolymerized-LMW-epiK5-N,O-sulfate or of a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutical carrier.

32. A pharmaceutical composition comprising, as active ingredient, a pharmacological active amount of an (epi)K5-amine-O-oversulfate-derivative having a sulfation degree of from 2 to 4, or of a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutical carrier.

33. The composition of claim 32, wherein said (epi)K5-amine-O-oversulfate-derivative is obtainable by treating a tertiary or quaternary organic base salt of an (epi)K5-N-sulfate-derivative with a O-sulfating agent under O-oversulfation conditions.

34. The composition of claim 32, wherein said (epi)K5-amine-O-oversulfate-derivative is obtainable by treating a tertiary or quaternary organic base salt of an (epi)K5-N-sulfate-derivative with a O-sulfating agent under O-oversulfation conditions, said salt with said organic base having been isolated immediately after its formation, at a pH of from about 5 to about 9.

35. The composition of claim 32, wherein said (epi)K5-amine-O-oversulfate-derivative is obtainable by

(a1') treating an (epi)K5-N-sulfate-derivative, in its acidic form, with a tertiary or quaternary organic base and isolating its salt with said tertiary or quaternary organic base immediately after its formation, at a pH of from about 5 to about 9;

(a2') treating said tertiary or quaternary organic base salt of said (epi)K5-N-sulfate-derivative with an O-sulfation agent under the conditions of an O-oversulfation and isolating the (epi)K5-amine-O-oversulfate-derivative as the sodium salt thereof which can subsequently be converted into another salt.